CENTERS FOR COMPLEMENTARY AND ALTERNATIVE MEDICINE RESEARCH

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P.T.

Office of Alternative Medicine
National Cancer Institute
National Heart, Lung and Blood Institute
National Institute of Arthritis and Musculoskeletal and Skin Disorders
National Institute of Dental Research
National Institute of Neurological Disorders and Stroke
National Institute on Aging

Letter of Intent Receipt Date: December 11, 1998
Application Receipt Date: January 22, 1999

PURPOSE

Despite the broad use of complementary and alternative medicine (CAM) treatments (Eisenberg et al., New England J. Med. 328: 246-352, 1993) there is a relative paucity of data available to demonstrate convincingly the safety, efficacy, effectiveness and mechanisms of these CAM practices. A similar conclusion was reached in a 1990 report on unconventional cancer treatments by the U.S. Office of Technology Assessment. This report urges a systematic analysis of alternative treatments and their effect on major disease, health and wellness (U.S. Office of Technology Assessment, OTA-H-405, 1990, p.225).

In order to promote high-quality research of CAM, the Office of Alternative Medicine (OAM), the National Cancer Institute (NCI), the National Heart, Lung and Blood Institute (NHLBI), the National Institute of Arthritis and Musculoskeletal and Skin Disorders (NIAMS), the National Institute of Dental Research (NIDR), National Institute of Neurological Disorders and Stroke (NINDS), and the National Institute on Aging (NIA) invite applications for Centers for CAM Research using the Specialized Center (P50) grant mechanism. Such Centers will provide the resources necessary for the rigorous scientific investigation of CAM. It is expected that research conducted at these Centers will examine the potential efficacy, effectiveness, safety and validity

of CAM practices, as well as the physiological or psychological mechanisms underlying these practices.

HEALTHY PEOPLE 2000

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2000," a PHS-led national activity for setting priority areas. This PA, Centers for Complementary and Alternative Medicine Research, is related to the priority areas of cancer, chronic disabling conditions, heart disease, infectious diseases, nutrition, oral health and stroke. Potential applicants may obtain a copy of "Healthy People 2000" (Full Report: Stock No. 017-001-00474-0 or Summary Report: Stock No. 017- 001-00473-1) through the Superintendent of Documents, Government Printing Office, Washington, DC 20402-9325 (telephone 202-512-1800).

ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic for-profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal government. Applications may include foreign components, but foreign organizations are not eligible to apply. To be considered, an applicant organization must have: (1) a minimum of three independent investigators who together represent experience in both basic and clinical research; (2) access to a patient care and service facility; and (3) three to six research projects that include at least one basic (mechanistic) study and one clinical study; Phase III trials and surveys will not be considered.

Although applications must be submitted from one institution, they may include subcontracted collaborative scientific arrangements with scientists from other institutions, including foreign institutions, as long as these arrangements are clearly delineated, and formally and officially confirmed by signed statements from the responsible officials of each institution. However, a full institutional commitment must come from the parent institution receiving the award.

NIH program staff listed under INQUIRIES should be consulted if there are questions regarding any of the above requirements or exclusions.

Applicants from institutions that have a General Clinical Research Center (GCRC) funded by the NIH National Center for Research Resources may wish to identify the GCRC as a resource for

conducting the proposed research. If so, a letter of agreement from either the GCRC Program Director or Principal Investigator should be included within the application.

MECHANISM OF SUPPORT

Support of this program will be through the NIH Specialized Center Grant (P50) mechanism. This mechanism supports the full range of research and development from basic to clinical and intervention studies. P50 Centers assemble critical masses of basic and clinical scientists to work together collaboratively. The essential characteristics of a P50 Center include: (1) a strong, focused scientific program encompassing basic and clinical research that will have a clear impact on human disease and associated quality-of-life or disability issues; (2) a strong, innovative program to establish and monitor developmental and feasibility studies that can respond quickly to new research opportunities; (3) a strong career development program to develop and expand the scientific cadre of investigators dedicated to research on a specific disease entity or biomedical problem; (4) shared core facilities that increase the functional capacity of the Center; and (5) a willingness and commitment to work with other Centers and scientists in order to maximize research progress.

Applicants will be responsible for the planning, direction, and execution of the proposed Center program. Awards will be administered under the PHS Grants Policy Statement. It is expected that another RFA similar to this one will be issued in FY 1999.

FUNDS AVAILABLE

The NIH anticipates making six to eight awards with an estimated commitment from the OAM of $10.5 million total costs for the initial year's funding. In addition, NCI, NHLBI, NIA, NIAMS, NIDR, and NINDS may provide support to meritorious applications that fit their program objectives. Funding levels are dependent on the receipt of applications of high technical and scientific merit, and the continued availability of funds. Because the nature and scope of applications may vary, it is anticipated that the award size will vary.

Applicants may request three to five years of support. An application submitted in response to this RFA is limited to $1.5 million total costs (direct and indirect) in the first year of the award. Future increases are limited to three percent per year.

Funding in response to this RFA is dependent upon the receipt of a sufficient number of applications of high scientific merit. Although this program is provided for in the financial plans of OAM, the award of grants pursuant to this RFA is contingent upon the availability of funds.

RESEARCH OBJECTIVES

1. Background

The demographics, prevalence, and patterns of use of CAM in the United States have been described (Eisenberg et al., New England J. Med. 328: 246-352, 1993). The most relevant findings are the following: a) extrapolation to the population of the United States suggests that Americans made approximately 425 million visits to providers of CAM therapy during 1990; and b) expenditures associated with CAM therapies appear similar to non-reimbursed expenses incurred for all hospitalizations in the United States. These findings indicate that CAM occupies a larger role in the health care of U.S. citizens than previously understood. Despite this broad use, there are, in general, insufficient scientific data that address safety and efficacy questions for CAM therapies.

The OAM currently supports three NIH P50 Centers for CAM Research. The Centers are designed to identify and evaluate promising CAM approaches by establishing mechanisms for investigators to have their research ideas reviewed, developed and executed in a scientifically rigorous manner. It is expected that work begun at the Centers will provide the basis for subsequent investigator-initiated research grant applications to the NIH.

2. Goals

A. General:

This RFA seeks to expand the current NIH Centers for CAM Research program with the addition of up to eight new P50 Centers. Centers for CAM Research will provide focal points for initiating and maintaining state-of-the-art research that will contribute to improved treatment and prevention of human disease, or that address the risk factors, rehabilitation or quality-of-life issues associated with these conditions. Centers will not only be expected to conduct a wide spectrum of research activities, but also to contribute significantly to the development of core research resources, career development of new investigators, and the expansion of the research base through collaborative research with scientists and clinicians (both CAM and conventional) in other institutions locally and nationwide.

Developmental research funds provide support for innovative developmental projects that take maximum advantage of new research opportunities, or that establish the methodological feasibility and strengthen the scientific rationale for proceeding to trials on the use of CAM. This provides a flexible means for responding quickly to new research opportunities. Career development of new and established investigators will generate a cadre of scientists who could leave the Center with research experience to develop independent CAM research programs.

In order to facilitate achievement of Center program goals, it is expected that each center will develop specialized multi-user resource activities, such as basic or clinical laboratories, database and data management facilities, or biostatistical cores.

Requirements for all Centers are annual meetings coordinated by the NIH Office of Alternative Medicine (OAM). The purposes of these meetings are to share scientific information, assess scientific progress, identify new research opportunities, and establish priorities that will accelerate the study of CAM.

B. Specific Objectives:

Specific objectives for the current Center applications include:

o Performing research related to CAM treatments in one of the listed research theme areas (see below);
o Investigating basic mechanisms of CAM therapeutic and diagnostic interventions;
o Conducting feasibility studies or Phase I and II trials of sufficiently developed CAM interventions for the purpose of developing randomized, controlled trials;
o Acting as an institutional focus for training in research methodology, bioethics, biostatistics, clinical trial design, epidemiology, health services studies and basic laboratory methods that relate to CAM;
o Providing a plan for establishing an advisory committee to provide program direction and advice to the Principal Investigator of the Center, including prioritization of developmental and feasibility studies, and utilization of core facilities;
o Developing a mechanism for scientific/technical merit review of developmental or feasibility studies from investigators;
o Developing workshops, seminars, etc. for training purposes; and
o Establishing a system to identify and support investigators in their career development;

Competing continuation (renewal) applications must demonstrate progress in the above areas as indicated by scientific progress, success in the initiation of competitively-supported research (both federal and non- federal sources of support can be applied to this criterion), the development of new CAM investigators, and collaborations with conventional scientists and CAM practitioners.

Research Activities

The overall goals and objectives of the Center's research agenda for the requested funding period should be explicitly stated in the application. This should include identification of the Center's research direction, as well as specific disease entities and target populations to be studied.

1. Research Theme Areas

Applicants should develop a multidisciplinary research focus that incorporates basic and clinical research in one of the following themes. The application should describe how the Research Theme will be integrated with one or more of the high priority CAM Program Areas (item 2).

A. Arthritis:

The overall goal of the Center will be to conduct and promote basic and clinical research on CAM approaches for the treatment of arthritis and related diseases, with emphasis on rheumatoid arthritis and osteoarthritis. Any of the relevant areas of CAM listed below (item 2: CAM Program Areas) could be included. The rationale for the choice of a particular CAM modality, as well as the reason for selection above other CAM modalities, should be provided. Selected CAM approaches may target prevention, modification of disease course, amelioration of clinical activity-symptoms (including pain), prevention of disability or rehabilitation. Multidisciplinary approaches to study the molecular and cellular basis of the mechanism of action of CAM therapies in arthritis are encouraged, as are collaborations with investigators doing basic research in arthritis. The establishment and use of animal and other models to study biological effect and mechanism of action of CAM approaches and agents are encouraged.

B. Asthma:

A number of CAM therapies have been reported to be of use in the treatment of asthma. However, controlled clinical trials are often lacking, and the mechanisms of action are not clearly understood. Further studies are needed to assess the efficacy of CAM remedies in allergic disease and asthma. Since the symptoms and clinical findings in chronic asthma fluctuate over time and can often appear to improve with placebo, larger, well-designed, double-blind, placebo-controlled trials appear warranted, as well as careful assessment of objective and immunological

endpoints. Although Phase III trials will not be considered for this RFA, applicants are encouraged to address methodological and other design issues necessary for the development of such trials. Moreover, the mechanism of action of these alternative therapies needs to be investigated and defined.

Examples of some potential areas of interest include the following:

Controlled studies are needed to evaluate the effectiveness of hypnotic suggestion in allergic disease and asthma and the pathophysiological pathway mediating the effects.

Controlled clinical trials are needed to evaluate the effectiveness of acupuncture in the treatment of asthma. The mechanisms mediating the effects of acupuncture on asthma require clarification.

Controlled clinical trails are necessary to assess the efficacy of homeopathy in asthma, and pharmacologic studies are necessary to identify the chemical agents and mechanisms of action.

Preliminary reports suggest that salt reduction and magnesium supplementation may have value in reducing asthmatic symptoms. Clinical trials appear warranted.

Herbal remedies, administered as powders or teas, have been popular. Controlled clinical trials are needed to assess their effectiveness, and pharmacologic studies are needed to determine their potential interactive effect with standard asthma medications.

Ayurvedic medicine is a complex system of health care consisting of numerous components that include transcendental meditation, herbal preparations, pulse diagnosis, and yoga. Studies of an Ayurvedic approach to asthma management, as well as studies of its separate components would be of considerable interest.

The rigorous study of breathing techniques (e.g., yoga breathing exercises such aspranayama; and diaphragmatic breathing) in asthma management would enhance understanding of asthma self-management techniques and their potential role in therapy.

C. Cancer:

Centers are sought to conduct and promote basic and clinical research on CAM approaches for the treatment of cancer. Any of the relevant areas of CAM listed below (item 2: CAM Program Areas) could be included. The rationale for the choice of a particular CAM modality, as well as the reason for selection above other CAM or non-CAM approaches, should be provided.

Research topics may target prevention, modification of disease course, supportive care or symptom management (including pain control), management of chemotherapy-, surgery- or radiation- induced side effects and issues involved in improving quality of life of cancer survivors. Multidisciplinary approaches to study the molecular and cellular basis of the mechanism of action of CAM therapies in cancer are encouraged, as are collaborations with investigators doing basic research in cancer. The establishment and use of animal and other models to study biological effect and mechanism of action of CAM approaches and agents is encouraged.

D. Craniofacial and Oral Disorders:

Craniofacial and oral diseases, and the approaches used by the public or professionals to improve oral health, provides unique opportunities for evaluating CAM interventions. The relative accessibility of the oral cavity and craniofacial structures allows non-invasive assessment of changes in tissue status or function, and thus, can be utilized to strengthen research on effects of CAM interventions.

Diseases and disorders that manifest in craniofacial and oral tissues include craniofacial anomalies, such as cleft lift and palate, oral and nasopharyngeal cancers; salivary and immunological disorders including Sjogrens Syndrome; aphthous ulcers and other soft tissue lesions; oral concomitants of HIV including oral candidiasis; acute dental pain associated with injury, infections, or treatments; and conditions such as TMJ, degenerative changes or masticatory muscle conditions which produce chronic pain or oral dysfunctions (jaw "locking" or difficulties in chewing), as well as two widely prevalent infectious diseases - dental caries and periodontal diseases.

Examples of some potential areas of interest include the following:

Studies evaluating the impact of CAM interventions (e.g., acupuncture, hypnosis) on pain or tissue repair following oral surgeries or dental procedures.

Studies on the use of CAM interventions to prevent, reduce, or manage persisting pain in oral-craniofacial tissues (e.g., TMJ and muscle pain)

Studies evaluating herbal, nutritional, pharmacological or other CAM therapies used to prevent or treat congenital or acquired craniofacial defects, oral diseases, or oral symptoms (e.g., preventing or managing oral candidiasis in HIV-positive individuals)

Studies evaluating the effects and properties (e.g., anti- microbial, anti-biofilm) of "chewing sticks," which are traditionally used for personal oral hygiene in many areas of the world

Studies to assess whether the use of bioelectromagnetic fields enhances prevention or treatment of infectious oral diseases involving oral microbial biofilms (e.g., dental caries, periodontal diseases)

E. Diseases or Disabilities Associated with the Elderly: Centers are sought to examine the use and effectiveness of alternative and complementary treatments that keep older people healthy, as well as help them manage their existing chronic illnesses and disabilities. There is special interest in health promotion and self management strategies, as well as specific treatments for age-related conditions and problems such as Alzheimer's disease, sleep, urinary incontinence, sexual dysfunction, problems associated with mobility and frailty, older women's health issues (including menopause), caregiving stresses, etc. More biological, clinical, and psychosocial research is needed on older people's use of, and effectiveness of, dietary supplements, herbal products, over-the- counter CAM medications, and other CAM treatments. Different types of studies are needed including: basic studies on factors affecting how older people and their caregivers make decisions about treatment utilization, research on the biological processes underlying treatment effectiveness, and applied studies examining medical and quality-of-life outcomes of the different CAM strategies.

F. HIV/AIDS:
Centers are sought to conduct and promote basic and clinical research on CAM approaches for the treatment and prevention of human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) and their sequelae, including opportunistic infections. Areas of interest include, but are not limited to: (1) treatment of primary HIV disease, (2) interventions designed to prevent transmission of HIV; (3) prophylaxis and treatment of opportunistic infections; and (4) the clinical management of symptoms and syndromes associated with HIV/AIDS, including pain, cachexia, nausea, fatigue and depression.

G. Neurological Disorders and Stroke
For most of the more serious common neurological disorders and stroke there are few treatments of demonstrated efficacy. Many neurological disorders are chronic, gradually progressive, and may cause persistent disability for years. Alternative therapies are desperately sought by patients.

Because of the complexity of brain function, clinical evaluation of the benefits of any therapy for chronic neurological disease is difficult to carry out. Applicants interested in CAM interventions for neurological disorders and stroke should design studies able to produce convincing pre-clinical evidence of the scientific basis of the intervention or design pilot clinical trials able to provide information required for subsequent large Phase III randomized clinical trials. Adequate statistical methodology and expertise should be apparent in all proposed studies (pre-clinical laboratory and pilot clinical studies). For all Centers evaluating neurological disorders and stroke, a statistical core with experience in appropriate long-term neurological outcomes is required for adequate experimental design and analysis of data. Applicants interested in investigating CAM approaches for treating neurological disorders and stroke should contact the NINDS Program Officers listed under INQUIRIES.

H. Sleep:
Identify fundamental mechanisms through which light (see "Bioelectromagnetics" below), food supplements (e.g. melatonin; also see Orthomolecular Medicine" below), and unconventional applications of exercise entrain sleep and circadian rhythms; alter sleep regulators (e.g. adenosine and immune system); and influence neural correlates of sleep including the transition between sleep and wakefulness, different stages of sleep, and sleep-related alterations in sensory perception and cognitive processing.

Investigate the risks, benefits, long-term safety, and efficacy of unconventional pharmacological, herbal and orthomolecular interventions and of unconventional applications of behavioral and psychotherapeutic interventions for sleep disturbances including obstructive sleep apnea, insomnia, parasomnias, narcolepsy, circadian rhythm sleep disorders, restless legs syndrome, and fibromyalgia; and to limit the effects of daytime sleepiness on performance in the workplace and classroom.

2. CAM Program Areas:

For the purpose of this RFA, investigators must include modalities from the following broad program areas in CAM:

o Alternative Medical systems (e.g., oriental medicine, Ayurvedic, Native American, homeopathy, naturopathy);

o Manipulative and body-based systems (e.g., chiropractic, osteopathic, massage therapy or unconventional applications of integrated conventional and physical therapies);

o Biofield (e.g., energy healing, intentional effects on living systems);

o Bioelectromagnetics (e.g., diagnostic and therapeutic application of electromagnetic fields including pulsed EM fields, magnetic fields, DC fields, artificial light therapy, etc. Note: This category does not include the study of electromagnetic fields as risk factors for disease);

o Pharmacologic Therapies (e.g., metabolic therapies, immunoaugmentative therapies as used by CAM practitioners or the public);

o Herbal Medicine (Note: This category does not include isolation of the active ingredients from herbal preparations for the purpose of drug development)

(Note: Studies incorporating the following three CAM program areas MUST focus on the more unconventional uses of these approaches and involve collaborations with expert practitioners of these approaches);

o Mind-Body Medicine: This RFA is limited to those mind-body approaches that address unconventional explanatory models with a focus on their NOVEL scientific and clinical use, or that are currently in use by the public or practitioners, usually outside of a conventional medicine setting (e.g., meditation, imagery, hypnosis, biofeedback, music therapy, yoga, spirituality, biological effects of consciousness). Mind-body approaches that are already integrated into conventional medicine (e.g., patient education, psychotherapy, cognitive-behavioral approaches, etc.) will NOT be considered;

o Health Promotion and Disease Prevention (e.g., unorthodox changes in lifestyle, including risk reduction, when applied as complete systems for chronic disease management [prevention and treatment] across multiple diagnostic categories);

o Orthomolecular Medicine: This category includes the use of products, many of which may be used as nutritional and food supplements (e.g., magnesium, Co-enzyme Q, carnitine, melatonin, DHEA, mega-doses of vitamins) when investigated for therapeutic or preventive purposes. These products are usually used in combinations and at very high doses well above the RDA. For the purposes of this RFA, orthomolecular medicine may be integrated within comprehensive lifestyle changes based on indigenous or non-orthodox systems of medicine (e.g., Ornish or Pritikin programs).

SPECIAL REQUIREMENTS

Each Center must include the following elements; applications that fail to meet these requirements will be considered unresponsive to the RFA and not reviewed:

1. A strong institutional commitment:

An institution receiving this award should incorporate the Center high within its institutional priorities. The institution should demonstrate a strong commitment to the program's stability and success. The application must provide a plan that addresses how the institutional commitment will be established and sustained, how it will maintain accountability for promoting scientific progress, and how the Center research effort will be given a high priority within the institution relative to other research efforts. This institutional commitment may be in the form of commitments to recruit scientific talent, provision of discretionary resources to the Center director, faculty appointments for Center investigators, assignment of research space, cost sharing of resources, or other ways to be proposed by the applicant.

2. A qualified Principal Investigator (PI):

A leader should be selected as Principal Investigator who can oversee and conduct planning activities and provide direction to the Center. The PI should have documented experience both as a scientist and as administrator of a research program. The PI is required to commit a minimum of 15% time to administration of Center activities and has to be primary investigator on one (but not more than two) subprojects.

3. Linkages to the CAM community:

The applicant needs to document that linkages to the relevant CAM communities exist and that CAM practitioners provide appropriate input to Center research projects.

4. A substantive patient population:

The grant application must demonstrate and document access to a patient population which can participate in and can benefit from the innovative clinical, community and population research activities of the Center.

5. Research projects:

Each Center application should include three to six research projects. Each of these projects must request at least three, but not more than five, years of support in the application. At least three of these submitted projects must be judged meritorious by the peer-review panel for the application to meet the minimal requirements of a P50 Center. Failure to meet this requirement will remove the application from funding consideration.

The research must be oriented toward the most critically needed areas of CAM research, and toward collaborative activities that address new innovative possibilities in CAM research. Whenever feasible, collaborations with appropriate CAM practitioners are required. Projects should be interactive with each other whenever possible. At least one of the approved subprojects has to be a basic (mechanistic) study and one has to be a clinical study other than a Phase III trial. Applications that do not meet this basic requirement will be ineligible for funding. While epidemiological and health services studies that can be completed in five years are permissible, surveys and Phase III trials WILL NOT be accepted under this RFA. Subproject principal investigators are required to commit at least 15% time to these projects.

Research components involving Phase I and II clinical trials must include provisions for rigorous data management, quality assurance, and auditing procedures. In addition, it is NIH policy that all clinical trials require data and safety monitoring, with the method and degree of monitoring being commensurate with the risks (NIH Notice #98-084). Funds should be budgeted for these activities. They should not duplicate internal review and monitoring systems that are already in place at the institution.

Collaborative arrangements within the Center, within the parent institution and with other institutions are encouraged. Collaborations with scientists outside the immediate Center should be documented with appropriate letters of commitment as applicable. Collaborations with other institutions, including foreign institutions, may involve subcontracting arrangements but an award will be made to one institution only; that institution is expected to demonstrate the full institutional commitment noted in 1. above.

6. Resource Cores:

A core is defined as a resource shared by multiple investigators that should enhance research productivity and increase the functional capacity of the Center. Subproject utilization of these cores is essential and needs to be specified in the application. At a minimum, the Center is required to have an administrative core that is responsible for the day-to-day administrative details, as well as program coordination and ongoing evaluation of the Center. Also falling within

the administrative core would be the Career Development Program, the Developmental Research Program and the Advisory Committee (items 7-9 below). Other cores that benefit the specific research activities of the Center may be added as appropriate. Examples of cores would include data management cores, biostatistical cores, clinical trial coordinating cores, and laboratory-based cores. These resources should not duplicate resources already available to Center investigators. However, fee-for-service cores (i.e., Center use of existing facilities) are acceptable with adequate justification.

7. Career Development:

The Center should demonstrate a consistent commitment to career development. Up to $150,000 (total costs) of the first year budget should be dedicated to the salaries and research activities of investigators who wish to pursue careers investigating alternative medicine. Candidates are expected to devote full-time to research and appropriate supplemental training. Recruitment should encourage the participation of qualified women and minorities where possible. To this end, each applicant should include a clear policy and plans for recruiting minorities and women. The Center application should propose the number of slots available, the criteria for eligibility and for selection of candidates, and describe the selection process. Also, the application should indicate prospective mentors who are already in place at the proposed Center, briefly describe their research programs, and describe complementary activities that contribute to the environment for career development (e.g., existing training grants, other career development mechanisms and relevant programs).

Career development research projects should adhere to the list of CAM program areas appearing in this announcement. Rebudgeting of Center funds to, or from, the career development program will be permitted only with prior program approval.

8. Developmental Research Program:

In each year of the award, Centers will allocate a minimum of $100,000 (total costs) to developmental and feasibility projects that explore innovative ideas, or that establish the methodological feasibility and strengthen the scientific rationale for proceeding to trials on the use of CAM. It is important that Centers use developmental funds to stimulate projects that take maximum advantage of new research opportunities. These projects may be collaborative among scientists within one or more Centers, or with scientists outside the Center environment. Developmental research projects should adhere to the list of CAM program areas appearing in

this announcement. Rebudgeting of Center funds to, or from, the developmental program will be permitted only with prior program approval.

It is not expected or required that feasibility and developmental projects will be identified by the time of submission. However, the Center application should include an institutional review process for supporting projects that represent the most innovative ideas and that are likely to have the greatest impact on CAM research. These funds are intended to remain flexible and to support feasibility and developmental studies of a limited duration (two years or less), rather than the duration of the entire grant period. The expectation is that successful feasibility studies will become fully developed projects within the Center, or funded through other forms of research support, e.g., R01.

9. Advisory Committee:

Scientific and administrative Center oversight is charged to a multidisciplinary Advisory Committee (AC) to be appointed by the Principal Investigator on a rotating basis. The AC shall not be chaired by the Principal Investigator who will serve in an ex officio capacity only. The AC should meet at least twice a year and minutes of the meeting should be kept. These minutes shall be made available to NIH staff upon request. The AC should consist of at least nine individuals familiar with the Center's research activities. The AC shall include both a biostatistician and epidemiologist to assist with the review of projects and the optimal approaches for subsequent data analysis. The AC shall have representation from the scientific, practitioner and lay communities in both CAM and conventional medicine. Members SHOULD NOT be identified until after an award is made. However, the process by which members will be chosen should be specified.

Besides prioritizing developmental and feasibility research projects submitted by Center or, if applicable, Consortium investigators, the AC should periodically review Center operations to ensure that Center resources, especially core facilities, are used for the most scientifically worthy projects. The AC should take an active role in encouraging younger faculty members to perform research and assist them in applying appropriate research concepts and methods. Support for the AC should be explicitly budgeted and justified.

10. Annual Meeting of Centers:

Centers will be expected to participate in annual meetings with OAM and IC staff to share positive and negative results with other Centers, share materials, assess progress, identify new research

opportunities, and establish interactions, research priorities and collaborations that will maximize the impact of the research. Travel funds for the Principal Investigator and selected Project Investigators may be budgeted for this purpose. This may include Project Investigators from other institutions who are actively collaborating with Centers investigators.

11. Investigational New Drug (or Device) applications (INDs):

It is the sole responsibility of the applicant to obtain all necessary clearances from the Food and Drug Administration as required. It is expected that applicants will have started the IND process, if required, well before submission. An initial FDA contact is listed under INQUIRIES. In addition, applicants are strongly encouraged to consult their local Institutional Review Boards (IRBs) concerning IND status and the IRB approval process.

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that women and members of minority groups and their subpopulations must be included in all NIH supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification is provided, that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43). All investigators proposing research involving human subjects should read the "NIH Guidelines For Inclusion of Women and Minorities as Subjects in Clinical Research," which have been published in the Federal Register of March 28, 1994 (FR 59 14508-14513), and in the NIH Guide for Grants and Contracts, Vol. 23, No. 11, March 18, 1994. Investigators may obtain copies from these sources or from the program staff listed under INQUIRIES. Program staff may also provide additional relevant information concerning the policy.

NIH POLICY AND GUIDELINES ON THE INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of NIH that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them. This policy applies to all initial (Type 1) applications submitted for receipt dates after October 1, 1998.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects"

that was published in the NIH Guide for Grants and Contracts, March 6, 1998, and is available at the following URL address: http://grants.nih.gov/grants/guide/notice-files/not 98-024.html

LETTER OF INTENT

Prospective applicants are asked to submit, by December 11, 1998, a letter of intent that includes a descriptive title of the overall proposed project; the name, address, telephone and FAX number of the Principal Investigator; the identities of other key personnel and participating institutions; and the number and title of this RFA. Although a letter of intent is not required, is not binding, and does not enter into the review of applications, the information that it contains will be especially helpful to the NIH in planning for the review of applications, estimating the potential workload, and avoiding conflicts of interest in the review process.

The letter of intent is to be sent to:

Dr. Richard L. Nahin
Office of Alternative Medicine
National Institutes of Health
Building 31, Room 5B-38
Bethesda, MD 20892-2182
FAX: (301) 480-3519 or (301) 594-6757

APPLICATION PROCEDURES

The research grant application form PHS Form 398 (rev. 5/95) is to be used in applying for this grant. These forms are available at most institutional offices of sponsored research and from the Division of Extramural Outreach and Information Resources, National Institutes of Health, 6701 Rockledge Drive, MSC 7910, Bethesda, MD 20892-7910, telephone 301/435-0714, Email: GrantsInfo@nih.gov; and may also be obtain on the World Wide Web at http://grants.nih.gov/grants/funding/phs398/phs398.html.

Prior to writing the application, applicants should carefully read the instructions provided with Form PHS 398 and this RFA.

The total page limitation of the application, as specified in the instructions of the Form PHS 398, does not apply to this RFA. Instead, the following stipulations apply:

Table of Contents:

Disregard the Table of Contents page from PHS 398 and, instead, write a Table of Contents appropriate for this Center grant application. The Table of Contents should list all items for which funding is sought, in addition to each specific activity required of the Center as outlined under "Special Requirements." Specifically list the locations of the checklist and the various supporting documents, including bibliographic sketches and other support pages. Each page of the application should be numbered consecutively. This numbering should be reflected in the Table of Contents.

Budget:

For preparation of the budget, the applicant should present a composite budget for all years of support. This composite budget should include the direct costs for each required Center activity (e.g., Advisory Committee, Developmental Research Program, Career Development, etc.), as well as each research project and each core facility. This composite budget should be in tabular format, with each budget year being listed in a separate column and each Center activity, core or subproject being listed in a separate row. Budget Form pages 4 and 5 of PHS Form 398 should be completed for each Center activity, core or subproject listed in the composite budget. These pages should be clearly labeled as to which Center activity, subproject or core they address.

Bibliographic Sketches:

Bibliographic sketches and other support pages are required for all proposed Center personnel and for all investigators associated with the research projects and cores. These pages should be in alphabetical order follow the budget pages and should not be duplicated in the descriptions of individual component projects and cores.

Research Projects and Core Facilities:

Applicants may use up to 25 pages to describe all required Center activities (including the Advisory Committee, the Developmental Research and Career Development Programs, the Administrative Core and the Center's overall goals and objectives) and up to 25 pages each for each of the research projects and for each core facility (excluding the Administrative Core), excluding bibliographies. Descriptions of the research projects and the core facilities should follow the PHS 398 format, section 9 (Research Plan). In addition, each project should provide a detailed description of core utilization and each core should document its contributions to Center research projects. Each of the six points listed under Human Subjects in the PHS 398 application must be addressed for those studies involving human subjects. Although not required at the time of the application, Institutional Review Board and Institutional Animal Care and

Use Committee approval must be obtained for each project listed, if appropriate, within 60 days of submission.

The RFA label available in the PHS 398 application package must be affixed to the bottom of the face page of the application. Failure to use this label could result in delayed processing of the application. In addition, the RFA title and number must be typed on line 2 of the face page of the application form and the YES box must be marked.

Submit a typewritten, signed original of the application, four signed photocopies, and the completed checklist in one package to:

CENTER FOR SCIENTIFIC REVIEW
NATIONAL INSTITUTES OF HEALTH
6701 ROCKLEDGE DRIVE, SUITE 1040 - MSC 7710
BETHESDA, MD 20892-7710
BETHESDA, MD 20817 (for express/courier service)

At the time of submission, one additional complete copy of the application must be sent to:

Dr. Richard L. Nahin
Office of Alternative Medicine
National Institutes of Health
Building 31, Room 5B-38
Bethesda, MD 20892-2182

Applications must be received by January 22, 1999. If an application is received after the date, it will be returned to the applicant without review. The Center for Scientific Review (CSR) will not accept any application that is essentially the same as one previously reviewed. This does not preclude the submission of a substantial revision of an application already reviewed, but such an application must follow the guidance in the Form PHS 398 application instructions for preparation of revised applications, including an introduction addressing the previous critique.

Individual subprojects from the P50 Center application may be simultaneously submitted to the CSR as investigator-initiated applications (e.g., R01); this fact must be clearly documented in the Center application under "pending support." If, following review, both the Center application and the R01 application are found to be in the fundable range, the subproject investigator must relinquish the R01 and will not have the option to withdraw from the Center grant. This is an NIH

policy intended to preserve the scientific integrity of a multi-project grant, which may be seriously compromised if a strong component project(s) is removed from the program. Investigators wishing to participate in a multi-project grant must be aware of this policy before making a commitment to the Principal Investigator and awarding institution.

REVIEW CONSIDERATIONS

Upon receipt, applications will be reviewed for completeness by the CSR and responsiveness by the OAM. Incomplete and/or unresponsive applications will be returned to the applicant without further consideration. In some cases, individual subprojects that are incomplete or unresponsive will be withdrawn from the review process while the remainder of the application goes through peer-review.

Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened by the CSR in accordance with NIH peer review procedures. As part of the initial merit review, all applications will receive a written critique and undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of applications under review, will be discussed, assigned a priority score, and receive a second level review by the appropriate National Advisory Council.

Review Criteria

All applications submitted in response to this RFA will be reviewed according to the following review criteria. Reviewers will consider these criteria when assigning a single overall score to each application. This single score should reflect their judgement that the proposed center will have a substantial impact on the pursuit of its goals.

Major factors to be considered in evaluation of applications will include:

1. How the proposed Center combines basic and clinical research into the scientific goals and research theme, as well as integration of appropriate CAM and conventional expertise;

2. If a competing continuation application, the quality and significance of the progress made in the previous funding period;

3. Scientific merit of each proposed subproject. Each research project will be reviewed according to the explicitly-stated set of five review criteria recently adapted by the NIH:

(a) Significance: Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

(b) Approach: Are the conceptual framework, design, methods, and analyses adequately developed, well-integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

(c) Innovation: Does the project employ novel concepts, approaches or methods?
Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

(d) Investigator: Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)?

(e) Environment: Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support

Each subproject will receive a priority score. The score reflects not only the feasibility of the project and the adequacy of the experimental design, but also the relevance to the overall goals of the Center and the appropriate utilization of Center resources (e.g., cores).

Each subproject also will be reviewed for the adequacy of plans to include both genders, minorities and their subgroups, and children as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects also will be evaluated.

In addition, the adequacy of the proposed protection for humans, animals or the environment will be evaluated to the extent they may be adversely affected by the project proposed in the application.

4. Scientific merit of combining the component parts into a Center;

5. Technical merit and justification of each core unit;

6. Adequacy of facilities to perform the proposed research, including laboratory and clinical facilities, instrumentation, and data management systems, when needed;

7. Adequacy of plans for interaction among investigators, and the integration of the various projects and core units;

8. Qualifications, experience and commitment of the PI and his/her ability to devote time and effort to provide effective leadership;

9. Scientific and administrative structure, including internal and external procedures for monitoring and evaluating the proposed research and for providing ongoing quality control and scientific review;

10. Institutional commitment to the program, and the appropriateness of resources and policies for the administration of a Center;

11. The proposed organization and activities of the Advisory Committee will be evaluated, including the process to prioritize developmental/feasibility research proposals and the process to chose Committee members after an award is made;

12. Career Development Program including adequacy of the process for selecting candidates for career development and plans for seeking out minority and women candidates; and adequacy of the individuals available to serve as possible mentors of career development candidates;

13. Developmental Research Program including adequacy of the proposed process for continuously reviewing and funding projects for their quality, innovativeness and potential impact; and potential of the program to generate innovative, high-quality projects on a consistent basis.

14. Demonstration of an effective relationship among Consortium institutions, including documentation of current relationships, as well as the functions, commitments and contributions each Consortium member will bring to the proposed Center;

15. The appropriateness of the budget for the proposed program and its individual components will be considered independently of the factors indicated above.

A single numerical priority score will be assigned to the application as a whole. Although primary emphasis will be placed on scientific merit, innovativeness, and past progress (where applicable), significant consideration will be given to administrative structure, multidisciplinary interactions, potential for impacting on the disease/condition in question, and institutional commitment.

AWARD CRITERIA

Applications recommended by the NIH Initial Review Group and by the appropriate national advisory council will be considered for award based on: 1) scientific and technical merit as determined by peer review; 2) program relevance and balance; 3) availability of funds; and 4) responsiveness to the goals and objectives of the RFA.

Schedule

Letter of Intent Receipt Date: December 11, 1998
Application Receipt Date: January 22, 1999
Review by Advisory Council: Aug/Sep 1999
Anticipated Award Date: September 1999

INQUIRIES

Inquiries concerning this RFA are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome.

Inquiries regarding programmatic issues may be directed to:

Dr. Patricia S. Bryant
Behavior, Oral Health Promotion, and Environment Program
National Institute of Dental Research
Natcher Building, Room 4AN-24E
Bethesda, MD 20892-6402
Telephone: (301) 594-2095
FAX: (301) 480-8318
Email: BryantP@de45.nidr.nih.gov

Dr. Cheryl A. Kitt
Programs in Pain, Neuroendocrinology, and Neurotoxicology

National Institute of Neurological Disorders and Stroke
7550 Wisconsin Avenue, Room 504
Bethesda, MD 20892
Telephone: (301) 496-1431
FAX: (301) 402-2060
Email: KittC@ninds.nih.gov

Dr. John R. Marler
Division of Stroke, Trauma and Neurodegenerative Diseases
National Institute of Neurological Disorders and Stroke
7550 Wisconsin Avenue, Room 800
Bethesda, MD 20892
Telephone: (301) 496-4226
FAX: (301) 480-1080
Email: MarlerJ@ninds.nih.gov

Dr. Richard L. Nahin
Office of Alternative Medicine
National Institutes of Health
Building 31, Room 5B-38
Bethesda, MD 20892-2182
Telephone: (301) 435-5042
FAX: (301) 402-4741 or (301) 594-6757
Email: NahinR@OD31EM1.OD.NIH.GOV

Dr. Marcia G. Ory
Social Science Research on Aging Program
National Institute on Aging
7201 Wisconsin Avenue, Suite 533, MSC 9205
Bethesda, MD 20892-9205
Telephone: (301) 402-4156
FAX: (301) 402-0051
Email: Marcia_Ory@NIH.GOV

Dr. Susana A. Serrate-Sztein
Rheumatic Diseases Program
National Institute of Arthritis and Musculoskeletal and Skin Diseases

45 Center Drive, Room 5AS-25E, MSC 6500
Bethesda, MD 20892-6500
Telephone: (301) 594-5032
FAX: (301) 480-4543
Email: szteins@exchange.nih.gov

Virginia S. Taggart, M.P.H
Division of Lung Diseases (Asthma)
National Heart, Lung and Blood Institute
6701 Rockledge Drive, Suite 10018, MSC 7952
Bethesda, MD 20892-7952
Telephone: (301) 435-0202
FAX: (301) 480-3557
Email: TaggartV@gwgate.nhlbi.nih.gov

Dr. Michael Twery
Division of Lung Diseases (Sleep)
National Heart, Lung and Blood Institute
6701 Rockledge Drive, Suite 10018, MSC 7952
Bethesda, MD 20892-7952
Telephone: (301) 435-0202
FAX: (301) 480-3557
Email: TweryM@gwgate.nhlbi.nih.gov

Dr. Jeffrey D. White
Division of Clinical Sciences
National Cancer Institute
Building 10, Room 3B38
Bethesda, MD 20892
Telephone: (301) 402-2912
FAX: (301) 402-1001
Email: jdwhite@helix.nih.gov

Although not a formal sponsor of this RFA, the Agency for Health Care Policy and Research encourages applications for the support of CAM research on patient outcomes, cost-effectiveness, health-related quality-of-life measures, types of providers, patients, treatments, and treatment settings. For more information, contact:

Dr. Mary A. Cummings
Center for Outcomes and Effectiveness Research
Agency for Health Care Policy and Research
2101 East Jefferson Street, Suite 605
Rockville, MD 20852
Telephone: (301) 594-1485
FAX: (301) 594-3211
Email: mcumming@ahcpr.gov

Although the National Institute of Mental Health (NIMH) is not a cosponsor of this RFA, applicants interested in research project grants concerning CAM approaches to treatment of mental disorders may contact:

Jerry Cott, Ph.D.
Division of Services and Intervention Research
National Institute of Mental Health
5600 Fishers Lane, Room 10-75
Rockville, MD 20857
Telephone: (301) 443-1185
FAX: (301) 594-6784
Email: jcott@helix.nih.gov

Inquiries regarding fiscal issues may be directed to:

Carol Fitzpatrick
Grants Management Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
45 Center Drive, Room 5AS-43B, MSC 6500
Bethesda, MD 20892-6500
Telephone: (301) 594-3503
FAX: (301) 480-4543
Email: fitzpatc@exchange.nih.gov

Martin R. Rubinstein
Grants Management Branch
National Institute of Dental Research
45 Center Drive, Room 4AN44A, MSC 6402

Bethesda, MD 20892-6402
Telephone: (301) 594-4800
FAX: (301) 480-8301
Email: mr49c@nih.gov

Karen D. Shields
Grants Management Branch
National Institute of Neurological Disorders and Stroke
Federal Building, Room 1004
Bethesda, MD 20892
Telephone: (301) 496-9231
FAX: (301) 402-0219
Email: ShieldsK@ninds.nih.gov

Marie Willett
Grants Operations Branch
National Heart, Lung and Blood Institute
6701 Rockledge Drive, Suite 7154, MSC 7926
Bethesda, MD 20892-7952
Telephone: (301) 435-0170
FAX: (301) 480-3310
Email: WillettM@gwgate.nhlbi.nih.gov

Inquiries regarding FDA issues may be directed to:

Dr. Freddie Ann Hoffman
Deputy Director, Medical Staff
Food and Drug Administration
5600 Fishers Lane, Room 15A08
Rockville, MD 20857
Telephone: (301) 827-6606
FAX: (301) 443-2446
Email: FHoffman@bangate.fda.gov

AUTHORITY AND REGULATIONS

The Office of Alternative Medicine (OAM) was mandated by Congress in 1991 and permanently established within the Office of the Director, National Institutes of Health (NIH), through the National Institutes of Health Revitalization Act (Public Law 103-43, Section 404E). The congressional language states that "the purpose of the Office is to facilitate the evaluation of alternative medical treatment modalities. . ." The language continues that "in carrying out subsection b [its purpose], the Director of the Office [of Alternative Medicine] shall - support research training - for which fellowship support is not provided under section 487."

This program is described in the Catalog of Federal Domestic Assistance Nos. 93.121, 93.213, 93.396, 93.837, 93.838, 93.846, 93.853, and 93.866. Awards are made under authorization of the Public Health Service Act, Title IV, Part A (Public Law 78-410, as amended by Public Law 99-158, 42 USC 241 and 285) and administered under PHS grants policies and Federal Regulations 42 FR 52 and 45 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

The PHS strongly encourages all grant and contract recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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